CLAIMS

[Claim(s)]
[Claim 1]A solution or dispersion liquid containing an adrenocorticotrophin derivative or its salt Inner aqueous phase, A manufacturing method of a sustained release drug producing a W/O type emulsified matter which makes an oil phase a solution containing biodegradation nature polymer which has a carboxyl group of isolation at the end, making an outer water phase distribute an emulsified matter subsequently obtained, producing a W/O/W type emulsified matter, and giving underwater desiccation.
[Claim 2]The manufacturing method according to claim 1 with which an outer water phase contains an osmoregulating chemical further.
[Claim 3]The manufacturing method according to claim 2 whose concentration of an osmoregulating chemical of an outer water phase is 0.1 thru/or 60% (W/V).
[Claim 4]The manufacturing method according to claim 2 whose osmoregulating chemical is polyhydric alcohol.
[Claim 5]The manufacturing method according to claim 2 whose osmoregulating chemical is mannitol.
[Claim 6]The manufacturing method according to claim 1 which is a lactic acid-glycolic acid copolymer whose composition ratios (mol %) of lactic acid/glycolic acid biodegradation nature polymer has a carboxyl group of isolation at the end, and are 100/0 thru/or 60/40.
[Claim 7]The manufacturing method according to claim 1 whose weight average molecular weight of a lactic acid-glycolic acid copolymer is 5,000 thru/or 20,000.
[Claim 8]An adrenocorticotrophin derivative is formula R^4-A^5-A^6-R^7.
[Benzyloxycarbonyl (Z) which combined R^4 via Nalpha among a formula, (C_2 - C_6)-alkanoyl, (C_6 - C_{10})-aryl (C_2 - C_4)-alkanoyl, . [whether it is cyclo alkanoyl which has an alkyl carbon atom up to two pieces, and 5-7 cycloalkyl carbon atoms, and] or R^1-A^2-A^3-A^4 (here -- A^4 -- Phe.) Mean Ala or Leu and A^3 means His, Ala, Phe, or D-Lys, A^2 means pyroglutamyl, Glu, D-Glu, or Ala, And a hydrogen atom which combined R^1 via Nalpha, Z, (C_2 - C_6)-alkanoyl, (C_6 - C_{10})-aryl (C_2 - C_4)-alkanoyl, Cyclo alkanoyl, (C_2 - C_4)-alkanoyl omega-amino-(C_5 - C_8)-n-alkanoyl which have an alkyl carbon atom up to two pieces, and 5-7 cycloalkyl carbon atoms, Methylsulfonyl omega-amino-(C_5 - C_8)-n-alkanoyl, 4-methylsulfonyl benzoyl, succinoil, a guru taro yl, (C_2 - C_4)-alkanoyl omega-amino-(C_3 - C_4)-n-alkanoyl, Methylsulfonyl omega-amino-(C_3 - C_4)-n-alkanoyl, A methylamide guru taro yl, H-Met, H-D-Met, and H-Met (O), H-D-Met (O), H-Met (O_2), and H-D-Met (O_2), H-Gly, Z-Gly, H-Tyr, Z-Tyr, or pyroglutamyl is meant -- it is. A^5 is D-Lys or Lys and A^6 Phenylalanine, It is N-methyl FERIRU alanine or 1,2,3,4-tetrahydroisoquinoline 3-carboxylic acid, And R^7 is NH-$(CH_2)_8$-NH_2, Gly-$(CH_2)_8$-NH_2, Gly-Lys-R^8, or Gly-D-Lys-R^8 (n is an integer of 4-10 here, and m is an integer of 2-6, and). and R^8 expresses 1-pylori NIJIRU, NH-R, or $N(R)_2$ (R is alkyl (C_1 - C_4)) -- it is -- the sustained release drug according to claim 1 which is peptide expressed with].
[Claim 9]The manufacturing method according to claim 1 whose adrenocorticotrophin

derivative is L-methionyl L-glutamyl L-histidyl L-phenylalanyl D-lysyl N-(8-aminooctyl)-L-phenylalaninamide S,S-dioxide.
[Claim 10]The manufacturing method according to claim 1 whose salt is acetate.
[Claim 11]The manufacturing method according to claim 1 whose sustained release drugs are injections.
[Claim 12]The manufacturing method according to claim 1 whose sustained release drug is a microcapsule.

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention]This invention relates to the manufacturing method of an adrenocorticotrophin derivative sustained release drug useful as psychotropic neural activity peptide. [0002]
[Description of the Prior Art]Poly (lactide/glycolide) (PLGA) of lactic acid/glycolic acid =50/50 is used as carrier material at JP,5-070363,A, and the manufacturing method by the spray drying process of the ****** biodegradability particle-like thing containing shrimp RACHIDO (Ebiratide) is indicated. The ACTH polymer controlled release system formed by carrying out a spray into the inactive gas which liquefied the mixture of adrenocorticotrophin (ACTH) and biocompatible polymer in the Patent Publication Heisei No. 507768 [seven to] gazette, and its manufacturing method are indicated. The incorporation rate of a drug rises and it is shown by by adding osmoregulating chemicals, such as mannitol, in a JP,6-145046,A item gazette at an outer water phase at the time of manufacture of the water-soluble drug by an underwater dry technique that an initial burst size decreases.
[0003]
[Problem(s) to be Solved by the Invention]An old man or a dementia patient is medicated with an adrenocorticotrophin derivative in many cases, and the dosing period becomes long, and the efforts relevant to the medication of the person himself/herself or a care worker or administration have a great thing. Therefore, intervals of administration are long and, moreover, the sustained release drug in which compliance is improved, especially injections are desired. Setting out of the release period of one month is desired from two weeks which is in agreement also with the medical checkup interval for a drug effect check, securing the drug release nature in the superfluous discharge and constant speed in early stages of after administration. However, the sustained release drug with which it is satisfied of said conditions is not known, but it is anxious for the manufacturing method which can produce the sustained release drug with which it is satisfied of said conditions.
[0004]
[Means for Solving the Problem]A result of having inquired wholeheartedly in view of such a situation in order for this invention persons to develop sustained-release injections over a long period of time of an adrenocorticotrophin derivative, W/O/W using lactic acid-glycolic acid (PLGA) which has composition ratio (mol %) and weight average molecular weight of a specific range If a sustained release drug is produced by an underwater dry technique from an emulsion, there being little initial discharge of an adrenocorticotrophin derivative and continuing for a long period of time -- zero -- it found out that a sustained release drug in which next discharge is shown was obtained. This invention was completed as a result of inquiring further wholeheartedly based on this knowledge. This invention a solution or dispersion liquid containing (1) adrenocorticotrophin derivative or its salt Namely, inner aqueous phase, A W/O type emulsified matter which makes an oil phase a solution containing biodegradation nature polymer which has a carboxyl group of isolation at the end is produced, Subsequently,

make an outer water phase distribute an emulsified matter obtained, and a W/O/W type emulsified matter is produced, A manufacturing method of a sustained release drug giving underwater desiccation, a manufacturing method of the above-mentioned (1) statement with which (2) outer water phases contain an osmoregulating chemical further, (3) A manufacturing method of the above-mentioned (2) statement whose concentration of an osmoregulating chemical of an outer water phase is 0.1 thru/or 60% (W/V), (4) A manufacturing method of the above-mentioned (2) statement whose osmoregulating chemical is polyhydric alcohol, (5) A manufacturing method of the above-mentioned (2) statement whose osmoregulating chemical is mannitol, (6) biodegradation -- a sex -- polymer -- an end -- isolation -- a carboxyl group -- having -- lactic acid -- /-- glycolic acid -- composition ratio (mol %) -- 100 -- /-- zero -- or -- 60 -- /-- 40 -- it is -- lactic acid - a glycolic acid copolymer -- it is -- the above -- (-- one --) -- a statement -- a manufacturing method. (7) A manufacturing method of the above-mentioned (1) statement whose weight average molecular weight of a lactic acid-glycolic acid copolymer is 5,000 thru/or 20,000, and (8) adrenocorticotrophin derivative are formula R^4-A^5-A^6-R^7. [Benzyloxycarbonyl (Z) which combined R^4 via Nalpha among a formula, (C_2 - C_6)-alkanoyl, (C_6 - C_{10})-aryl (C_2 - C_4)-alkanoyl, . [whether it is cyclo alkanoyl which has an alkyl carbon atom up to two pieces, and 5-7 cycloalkyl carbon atoms, and] or R^1-A^2-A^3-A^4 (here -- A^4 -- Phe.) Mean Ala or Leu and A^3 means His, Ala, Phe, or D-Lys, A^2 means pyroglutamyl, Glu, D-Glu, or Ala, And a hydrogen atom which combined R^1 via Nalpha, Z, (C_2 - C_6)-alkanoyl, (C_6 - C_{10})-aryl (C_2 - C_4)-alkanoyl, Cyclo alkanoyl, (C_2 - C_4)-alkanoyl omega-amino-(C_5 - C_8)-n-alkanoyl which have an alkyl carbon atom up to two pieces, and 5-7 cycloalkyl carbon atoms, Methylsulfonyl omega-amino-(C_5 - C_8)-n-alkanoyl, 4-methylsulfonyl benzoyl, succinoil, a guru taro yl, (C_2 - C_4)-alkanoyl omega-amino-(C_3 - C_4)-n-alkanoyl, Methylsulfonyl omega-amino-(C_3 - C_4)-n-alkanoyl, A methylamide guru taro yl, H-Met, H-D-Met, and H-Met (O), H-D-Met (O), H-Met (O_2), and H-D-Met (O_2), H-Gly, Z-Gly, H-Tyr, Z-Tyr, or pyroglutamyl is meant -- it is. A^5 is D-Lys or Lys and A^6 Phenylalanine, It is N-methyl FERIRU alanine or 1,2,3,4-tetrahydroisoquinoline 3-carboxylic acid, And R^7 is NH-$(CH_2)_8$-NH_2, Gly-$(CH_2)_8$-NH_2, Gly-Lys-R^8, or Gly-D-Lys-R^8 (n is an integer of 4-10 here, and m is an integer of 2-6, and). and R^8 expresses 1-pylori NIJIRU, NH-R, or $N(R)_2$ (R is alkyl (C_1 - C_4)) -- it is -- a sustained release drug of the above-mentioned (1) statement which is peptide expressed with]. (9) A manufacturing method of the above-mentioned (1) statement whose adrenocorticotrophin derivative is L-methionyl L-glutamyl L-histidyl L-phenylalanyl D-lysyl N-(8-aminooctyl)-L-phenylalaninamide S,S-dioxide, (10) It is related with a manufacturing method of the above-mentioned (1) statement whose salt is acetate, a manufacturing method of the above-mentioned (1) statement whose (11) sustained release drugs are injections, and a manufacturing method of the above-mentioned (1) statement whose (12) sustained release drugs are microcapsules.

[0005]When displaying by a cable address about amino acid used by this invention, IUPC-IUB commission OBU biochemical no MENKU lecher (Commission on BiochemicalNomencleture) (European journal OBU biochemistry (European.)) Especially when there may be an optical isomer based on a cable address by the 138th volume of Journal ofBiochemistry, 9 - 37 pages, and 1984, or a conventional cable address in an applicable field, L object shall be shown if not shown clearly.

[0006]As an adrenocorticotrophin derivative (it may only carry out abbreviated to a derivative hereafter) used by this invention, it is constituted by four or more peptide and the molecular weight 500 [about] - about 100,000 thing are mentioned. or [that internal secretion ability is weak as an example of this derivative, for example] -- or what does not have but has a central action is mentioned. Specifically, it is formula R^4-A^5-A^6-R^7(I) given in JP,7-5632,B.

[Benzyloxycarbonyl (Z) which combined R^4 via Nalpha among a formula, (C_2 - C_6)-alkanoyl, (C_6 - C_{10})-aryl (C_2 - C_4)-alkanoyl, . [whether it is cyclo alkanoyl which

has an alkyl carbon atom up to two pieces, and 5-7 cycloalkyl carbon atoms, and] or R^1-A^2-A^3-A^4 (here -- A^4 -- Phe.) Mean Ala or Leu and A^3 means His, Ala, Phe, or D-Lys, A^2 means pyroglutamyl, Glu, D-Glu, or Ala, And a hydrogen atom which combined R^1 via Nalpha, Z, (C_2 - C_6)-alkanoyl, (C_6 - C_{10})-aryl (C_2 - C_4)-alkanoyl, Cyclo alkanoyl, (C_2 - C_4)-alkanoyl omega-amino-(C_5 - C_8)-n-alkanoyl which have an alkyl carbon atom up to two pieces, and 5-7 cycloalkyl carbon atoms, Methylsulfonyl omega-amino-(C_5 - C_8)-n-alkanoyl, 4-methylsulfonyl benzoyl, succinoil, a guru taro yl, (C_2 - C_4)-alkanoyl omega-amino-(C_3 - C_4)-n-alkanoyl, Methylsulfonyl omega-amino-(C_3 - C_4)-n-alkanoyl, A methylamide guru taro yl, H-Met, H-D-Met, and H-Met (O), H-D-Met (O), H-Met (O_2), and H-D-Met (O_2), H-Gly, Z-Gly, H-Tyr, Z-Tyr, or pyroglutamyl is meant -- it is. A^5 is D-Lys or Lys and A^6 Phenylalanine, It is N-methyl FERIRU alanine or 1,2,3,4-tetrahydroisoquinoline 3-carboxylic acid, And R^7 is NH-$(CH_2)_8$-NH_2, Gly-$(CH_2)_8$-NH_2, Gly-Lys-R^8, or Gly-D-Lys-R^8 (n is an integer of 4-10 here, and m is an integer of 2-6, and). and R^8 expresses 1-pylori NIJIRU, NH-R, or $N(R)_2$ (R is alkyl (C_1 - C_4)) -- it is -- peptide expressed with] is mentioned.

[0007]In compound (I), R^4 is Z, phenyl-(C_2 - C_4)-alkanoyl (an example, phenylacetyl, etc.), and (C_2 - C_6)-alkanoyl (an example, acetyl, etc.) preferably. R^1 -- desirable -- a hydrogen atom, Z, and phenyl-(C_2 - C_4)-alkanoyl (an example.) (C_2 - C_6)-alkanoyl (an example.), such as phenylacetyl Acetyl-epsilon-amino caproyl, such as acetyl, methylsulfonyl epsilon-amino caproyl, 4-methylsulfonyl benzoyl, a guru taro yl, acetyl-beta-alanyl, They are methyl-sulfonyl beta-alanyl, a methylamide guru taro yl, H-Met, H-Met (O), H-D-Met (O), H-Met (O_2), H-Gly, Z-Gly, H-Tyr, Z-Tyr, and pyroglutamyl. R^1 is H-Met (O), H-Met (O_2), and HO_2C-$(CH_2)_3$-CO- especially preferably. In compound (I), sulfinyl groups of residue H-Met (O) are R-arrangement and S-arrangement. A^5 is D-Lys preferably. A^6 means phenylalanine, N-methylphenyl alanine, or 1,2,3,4-tetrahydroisoquinoline 3-carboxylic acid, and its L-arrangement is preferred respectively in that case. A^6 is phenylalanine especially preferably.

[0008]Although basic C-end residue R^7 in particular is not limited, it is -NH-$(CH_2)_n$-NH_2 preferably. in that case, n -- desirable -- 6 thru/or 10 -- it is 8 especially preferably. A partial sequence of desirable compound (I) is shown below.

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Glu-His-Phe-D-Lys-Phe--Ala-Ala-Phe-D-Lys-Phe--Glu-Ala-Phe-D-Lys-Phe-compound (I) preferably, H-Met(O)-Glu-His-Phe-D-Lys-Phe-NH-$(CH_2)_8$-NH_2,
H-Met(O)-Glu-His-Phe-D-Lys-Phe-NH-$(CH_2)_6$-NH_2,
H-Met(O_2)-Glu-His-Phe-D-Lys-Phe-NH-$(CH_2)_8$-NH_2,
H-Met(O_2)-Ala-Ala-Phe-D-Lys-Phe-NH-$(CH_2)_8$-NH_2, And it is HOOC-$(CH_2)_3$-CO-Glu-Ala-Phe-D-Lys-Phe-NH-$(CH_2)_8$-NH_2. It has a sulfinyl group of S- or R-arrangement in each.

[0009]Compound (I) is following formula
H-Met(O_2)-Glu-His-Phe-D-Lys-Phe-NH-$(CH_2)_8$-NH_2 especially preferably. It is shrimp RACHIDO expressed with [L-methionyl L-glutamyl L-histidyl L-phenylalanyl D-lysyl N-(8-aminooctyl)-L-phenylalaninamide S,S-dioxide].

[0010]Shrimp RACHIDO is the 4th thru/or the 9th peptide fragments from an amino terminal part of ACTH which embellished a C terminal of ACTH with 8-amino-n-octylamine, it passes through a blood brain barrier and it is shown clearly that it shifts at least to each part of the inside of a brain. Since the metabolic rate of shrimp RACHIDO becomes slow about 5 times within about 3 times and a brain in a blood serum compared with a non-modulator of a C terminal and it has almost no internal secretion ability, ACTH is a different substance.

[0011]compound (I) or its salt -- the very thing -- it can manufacture by a publicly known method. As such a method, a method of being similar to a method of JP,7-5632,B, Journal of Medicinal Chemistry (Journal of Medicinal Chemistry), 35 volumes, 3942 pages, and a statement [1992] or this, for example is mentioned. A salt permitted pharmacologically preferably is used as a salt of compound (I). As such a salt,

a salt with inorganic acid (an example, chloride, sulfuric acid, nitric acid, etc.), organic acid (an example, carbonic acid, GCC acid, succinic acid, acetic acid, propionic acid, trifluoroacetic acid, etc.), etc. is mentioned. It is a salt with organic acid (an example, carbonic acid, GCC acid, succinic acid, acetic acid, propionic acid, trifluoroacetic acid, etc.) still more preferably. It is a salt with acetic acid especially preferably. These salts may be any of MONO thru/or the Tori salt. They are JI thru/or the Tori salt preferably. A derivative used by this invention may be used as it is, or may be used as a salt.

[0012]Biodegradation nature polymer which has a carboxyl group of isolation at the end used by this invention is biodegradation nature polymer a number average molecular weight by GPC measurement and whose number average molecular weight by the end group determination correspond mostly. A number average molecular weight by the end group determination is computed as follows. About 1 thru/or 3 g of biodegradation nature polymer are dissolved in a mixed solvent of acetone (25 ml) and methanol (5 ml), A carboxyl group in this solution is promptly titrated by using phenolphthalein as an indicator with a bottom of churning 0.05N alcoholic pottasium hydroxide solution in a room temperature (20 **), and a number average molecular weight is computed from a following formula.

Number-average-molecular-weight =20000xA/BA by the end group determination:

Mass (g) of biodegradation nature polymer

B: Quantity of a 0.05N alcoholic pottasium hydroxide solution added even to a titration end point (ml)

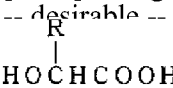
For example, it is compounded by a non-catalyst dehydration polycondensation method from one or more kinds of alpha-hydroxy acids, and a number average molecular weight by GPC measurement and a number average molecular weight by an end fixed quantity are mostly in agreement in a polymer which has a carboxyl group of isolation at the end. On the other hand, it is compounded by a ring-opening-polymerization method using a catalyst from a cyclic dimer, and a number average molecular weight by the end group determination far exceeds a number average molecular weight by GPC measurement in a polymer which does not have a carboxyl group of isolation substantially at the end. A polymer which has a carboxyl group of isolation at the end according to this difference is clearly distinguishable from a polymer which does not have a carboxyl group of isolation at the end.

[0013]A number average molecular weight according to GPC measurement to a number average molecular weight by the end group determination being an absolute value is a relative value changed with various analysis and analysis conditions (for example, selection of a kind of mobile phase, a kind of column, a primary standard, and slice width, selection of a baseline, etc.). Therefore, although correlation by both most important numerical value is difficult, for example, that a number average molecular weight by GPC measurement and a number average molecular weight by the end group determination are mostly in agreement, A number average molecular weight by the end group determination says that they are about 1.5 times [about 0.8 to] as many ranges still more preferably twice [about] from about 0.5 time preferably twice [about] from about 0.4 time of a number average molecular weight by GPC measurement. That a number average molecular weight by the end group determination far exceeds a number average molecular weight by GPC measurement means that a number average molecular weight by the end group determination exceeds the twice [about] of a number average molecular weight by GPC measurement.

[0014]As an example of biodegradation nature polymer of having a carboxyl group of isolation at the end, For example, alpha-hydroxycarboxylic acid (an example, glycolic acid, lactic acid, hydroxybutyric acid, etc.). hydroxydicarboxylic acid and hydroxy tricarboxylic acid (an example, malic acid, etc.) (an example.) A polymer compounded by non-catalyst dehydration polycondensation from one or more sorts, such as citrate Hitoshi, Copolymers or these mixtures, Polly alpha-cyanoacrylic ester, polyamino acid, maleic anhydride (example, Polly gamma-benzyl-L-glutamic acid, etc.) system

copolymers (an example, a styrene maleic acid copolymer, etc.), etc. are mentioned. biodegradation nature polymer -- desirable -- aliphatic polyester (an example.), for example, alpha-hydroxycarboxylic acid A polymer compounded by non-catalyst dehydration polycondensation from one or more sorts, such as hydroxydicarboxylic acid, hydroxy tricarboxylic acid (an example, malic acid, etc.), etc. (an example, citrate, etc.), such as glycolic acid, lactic acid, and hydroxybutyric acid, copolymers, or these mixtures are mentioned. Any of randomness, a block, and a graft may be sufficient as form of a polymerization. When above-mentioned alpha-hydroxy acids, hydroxydicarboxylic acid, and hydroxy tricarboxylic acid have an optical activity center in intramolecular, both D- L- and DL-object can be used.

[0015]biodegradation nature polymer which has a carboxyl group of isolation at the end -- desirable -- a (1) lactic-acid-glycolic acid copolymer or (2) and (A) glycolic acid, and



(II)

It is the biodegradation nature polymer which mixed a copolymer with the hydroxycarboxylic acid shown by (R expresses the alkyl group of the carbon numbers 2-8 among a formula), and (B) polylactic acid. The biodegradation nature polymer which has a carboxyl group of isolation at the end is a lactic acid-glycolic acid copolymer especially preferably.

[0016]When using a lactic acid-glycolic acid copolymer as biodegradation nature polymer, the composition ratio (lactic acid/glycolic acid) (mol %) changes with release periods, but in the case of two weeks thru/or one month, release periods are 100/0 thru/or 60/40, for example. composition ratio -- desirable -- 90/10 thru/or 70/30 -- further -- desirable -- 85/15 thru/or 70/30 -- it is 85/15 thru/or 75/25 especially preferably. The weight average molecular weight of this lactic acid-glycolic acid copolymer is generally 5,000 thru/or 20,000. weight average molecular weight -- further -- desirable -- 8,000 thru/or 19,000 -- it is 10,000 to 18,000 especially preferably. The degree of dispersion (weight average molecular weight/number average molecular weight) of this lactic acid-glycolic acid copolymer is about 1.2 to about 4.0 preferably. A degree of dispersion is about 1.5 to about 3.5 still more preferably. The above-mentioned lactic acid-glycolic acid copolymer can be manufactured in accordance with a publicly known manufacturing method, for example, a manufacturing method given in JP,61-28521,A.

[0017]The above-mentioned formula [II]As an alkyl group of a straight chain of the carbon numbers 2-8 shown by R inside, or a letter of branching, For example, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl one, tert-pentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl, etc. are mentioned. Preferably, an alkyl group of a straight chain of the carbon numbers 2-5 or a letter of branching is used. As an example, ethyl, propyl, isopropyl, butyl, isobutyl, etc. are mentioned, for example. R is ethyl especially preferably.

[0018]As hydroxycarboxylic acid shown by said formula (II), 2-hydroxybutyric acid, 2-hydroxyvaleric acid, 2-hydroxy-3-methylbutyric acid, 2-hydroxycaproic acid, 2-hydroxyisocaproic acid, 2-hydroxycapric acid, etc. are mentioned, for example. Among these [especially], 2-hydroxybutyric acid, 2-hydroxyvaleric acid, 2-hydroxy-3-methylbutyric acid, and 2-hydroxycaproic acid are preferred. Hydroxycarboxylic acid shown by formula (II) is 2-hydroxybutyric acid especially preferably. Although any of D-object, L-object and D, and L-object may be sufficient as these hydroxycarboxylic acid, D-object / L-object (mol %) does not have about 75/25, and its thing of the range of 75 is preferred about 25/. Still more preferably, D-object / L-object (mol %) does not have about 60/40, and is hydroxycarboxylic acid of the range of 60 about 40/. Especially preferably, D-object / L-object (mol %) does not have about 55/45, and is hydroxycarboxylic acid of the range of 55 about 45/.

[0019]In a copolymer (it is hereafter called a glycolic acid copolymer (A) for short) with hydroxycarboxylic acid shown by glycolic acid and formula (II), any of randomness, a block, and a graft may be sufficient as form of copolymerization. Preferably, it is a random copolymer. Hydroxycarboxylic acid which is formula (II) and is shown may be used at one sort or a rate proper two or more sorts. Composition ratio with hydroxycarboxylic acid shown by glycolic acid and formula (II) in a glycolic acid copolymer (A) has a preferred case where glycolic acid is % and about 10 thru/or the about 75-mol remainder are hydroxycarboxylic acid. It is a case where glycolic acid is about 20 thru/or about 75-mol %, and the remainder is hydroxycarboxylic acid, still more preferably. It is a case where glycolic acid is about 40 thru/or about 70-mol %, and the remainder is hydroxycarboxylic acid, especially preferably. As for these glycolic acid copolymers, about 2,000 to about 50,000 thing is used for weight average molecular weight. Weight average molecular weight is about 3,000 to about 40,000 preferably. Weight average molecular weight is about 8,000 to about 30,000 still more preferably. A degree of dispersion (weight average molecular weight/number average molecular weight) of these glycolic acid copolymers is about 1.2 to about 4.0 preferably. A degree of dispersion is about 1.5 to about 3.5 especially preferably. The above-mentioned glycolic acid copolymer (A) can be manufactured in accordance with a publicly known manufacturing method, for example, a method given in JP,61-28521,A.

[0020]As polylactic acid, although any of L-object, D-objects, and these mixtures may be sufficient, D-object / L-object (mol %) does not have about 75/25, and a thing of the range of 80 is preferred about 20/. Still more preferably, D-object / L-object (mol %) does not have about 60/40, and is polylactic acid of the range of 75 about 25/. Especially preferably, D-object / L-object (mol %) does not have about 55/45, and is polylactic acid of the range of 75 about 25/. Weight average molecular weight of this polylactic acid is about 1,500 to about 30,000 preferably. Weight average molecular weight is about 2,000 to about 20,000 still more preferably. Weight average molecular weight is about 3,000 to about 15,000 especially preferably. A degree of dispersion of polylactic acid is about 1.2 to about 4.0 preferably. A degree of dispersion is about 1.5 to about 3.5 especially preferably. About a manufacturing method of polylactic acid, a method of carrying out ring opening polymerization of RAKUCHIDDO which is a dimer of lactic acid, and a method of carrying out dehydration polycondensation of the lactic acid are known. In order [which is used by this invention] to obtain polylactic acid of low molecular weight comparatively, a method of carrying out dehydration polycondensation of the lactic acid directly is preferred. This manufacturing method is indicated, for example to JP,61-28521,A.

[0021]The mixture ratio (% of the weight) expressed with (A)/(B), for example does not have about 10/90, and a glycolic acid copolymer (A) and about 90/of polylactic acid (B) are used in 10. The mixture ratio (% of the weight) is about 20/80 thru/or about 80/20 preferably. The mixture ratio (% of the weight) is about 30/70 thru/or about 70/30 still more preferably. With weight average molecular weight in this specification, and a degree of dispersion. Polystyrene whose weight average molecular weight is nine kinds, 120,000, 52,000, 22,000, 9,200, 5,050, 2,950, 1,050, 580, and 162, is used as a primary standard. A molecular weight and a computed degree of dispersion of polystyrene conversion measured with gel permeation chromatography (GPC) are said. Measurement used chloroform for GPC column KF804Lx2 (made by Showa Denko), and the RI monitor L-3300 (made by Hitachi) as use and a mobile phase.

[0022]When it is considered as solution as an osmoregulating chemical used by this invention, as long as osmotic pressure is shown, it may be what kind of substance. As an example of this osmoregulating chemical, water-soluble polyhydric alcohol class, water-soluble monohydric alcohol, water-soluble monosaccharide, disaccharide and oligosaccharide or those derivatives, water-soluble amino acid, water-soluble peptide, protein, or those derivatives etc. are mentioned, for example.

[0023]As the water-soluble above-mentioned polyhydric alcohol class, hexahydric alcohol, such as pentavalent alcohols, such as dihydric alcohol, such as glycerin, arabitol, xylitol, and adonitol, mannitol, sorbitol, and dulcitol, is mentioned, for example. Alcohols of 6 values are [among these] preferred. Especially, especially mannitol is preferred. As the water-soluble above-mentioned monohydric alcohol, methanol, ethanol, isopropyl alcohol, etc. are mentioned, for example. Ethanol is [among these] preferred. As the water-soluble above-mentioned monosaccharide, hexose, such as pentose, such as arabinose, xylose, and ribose .2-deoxyribose, grape sugar, fructose, galactose, mannose, a sorbose, rhamnose, and fucose, is mentioned, for example. Hexose is [among these] preferred. As the water-soluble above-mentioned disaccharide, maltose, cellobiose, alpha, and alpha-trehalose, milk sugar, sucrose, etc. are mentioned, for example. Milk sugar and sucrose are [among these] preferred. As the water-soluble above-mentioned oligosaccharide, tetrasaccharides, such as trisaccharides, such as a maltotriose and raffinose, and a stachyose, etc. are mentioned, for example. Trisaccharide is [among these] preferred. As a derivative of the water-soluble above-mentioned monosaccharide, disaccharide, and oligosaccharide, glucosamine, galactosamine, glucuronic acid, galacturonic acid, etc. are mentioned, for example.

[0024]As amino acid of the above-mentioned solution, for example Neutral amino acid, such as a glycine, an alanine, valine, leucine, isoleucine, phenylalanine, tyrosine, tryptophan, serine, threonine, proline, hydroxyproline, cystein, and methionine, an iron permanent wave -- basic amino acid, such as acidic amino acid, such as RAGIN acid and glutamic acid, lysine, arginine, and histidine, etc. are mentioned. Acid (an example, chloride, sulfuric acid, phosphoric acid, etc.) of these water-soluble amino acid or a salt with alkali (alkaline metals, such as an example, sodium, and potassium etc.) may be used. As water-soluble peptide, protein, or those derivatives, casein, globulin, prolamin, albumin, gelatin, etc. are mentioned, for example. Water-soluble polyhydric alcohol class and water-soluble monosaccharide, disaccharide and oligosaccharide, or those derivatives are preferred among the above-mentioned osmoregulating chemicals. A water-soluble polyhydric alcohol class and water-soluble monosaccharide are still more preferred. It is mannitol at a water-soluble, especially desirable polyhydric alcohol class and a concrete target.

[0025]These osmoregulating chemicals may be used alone, or may mix and use two or more sorts. When an osmoregulating chemical is a nonionic substance, concentration in inside of an outer water phase of these osmoregulating chemicals does not have about 0.1%, does not have about 60% (W/V) of about 0.5% preferably, and is about 1% thru/or about 10% (W/V) more preferably about 30% (W/V). When an osmoregulating chemical is an ionic substance, concentration which **(ed) the above-mentioned concentration by the whole ionic valency is used. The addition concentration of an osmoregulating chemical does not need to be below solubility, and a part may be a dispersion state.

[0026]Below, a manufacturing method of this invention is explained in full detail. First, a derivative or its salt (it may carry out abbreviated to a drug hereafter) is dissolved or distributed in water, If required for this, drug maintenance substances, such as gelatin, agar, poly vinyl alcohol, or basic amino acid (for example, arginine, histidine, lysine), will be added, and it will be dissolved or suspended, and will be considered as inner aqueous phase. Concentration of a drug in inner aqueous phase is about 0.1 thru/or about 150% (W/V) preferably. They are about 20 thru/or about 130% (W/V) still more preferably. They are about 60 thru/or about 120% (W/V) especially preferably. In inner aqueous phase, carbonic acid, acetic acid, oxalic acid, citrate, phosphoric acid, chloride, etc. may add sodium hydroxide, arginine, lysine, those salts, etc. as a pH adjuster for maintaining the stability of a drug, and solubility. As a stabilizing agent of a drug, albumin, gelatin, citrate, As polyol compounds, such as sodium ethylenediaminetetraacetate, dextrin, sodium hydrogen sulfite, and a polyethylene

glycol, or a preservative, P-hydroxybenzoate esters (methylparaben, propylparaben, etc.), benzyl alcohol, chlorobutanol, a thimerosal, etc. which are generally used may be added.

[0027]Thus, it adds into a solution (oil phase) containing biodegradation nature polymer (it may carry out abbreviated to polymer hereafter) which has a carboxyl group of isolation of obtained inner aqueous phase at the end, subsequently emulsification operation is performed, and a W/O type emulsified matter is manufactured. This emulsification operation is performed by method by mixers, such as a publicly known dispersion method, for example, intermittence vibration, a propeller type agitator, or a turbine type agitator, the colloid mill method, the homogenizer method, an ultrasonic irradiation method, etc. That by which a solution (oil phase) containing the above-mentioned polymer dissolved this polymer in an organic solvent which is not substantially mixed with water is used. Solubility to water of this organic solvent is below 3% (W/W) at ordinary temperature (20 **) preferably. As for the boiling point of an organic solvent, it is preferred that it is 120 ** or less. As an organic solvent, for example Halogenated hydrocarbon (an example, dichloromethane, chloroform, chloroethane, trichloroethane, carbon tetrachloride, etc.), With a carbon numbers of three or more alkyl ether, alkyl (four or more carbon numbers) ester (an example, butyl acetate, etc.) of fatty acid (an example, isopropyl ether, etc.), aromatic hydrocarbon (an example, benzene, toluene, xylene, etc.), etc. are mentioned. These may be mixed and used at a rate proper two or more sorts. Organic solvents are halogenated hydrocarbon (an example, dichloromethane, chloroform, chloroethane, trichloroethane, a carbon tetrachloride, etc.) still more preferably. An organic solvent is dichloromethane especially preferably. Although concentration of polymer in an oil phase changes with a molecular weight of this polymer, and kinds of solvent, it is about 0.01 thru/or about 80% (W/W) preferably. They are about 0.1 thru/or about 70% (W/W) still more preferably. They are about 1 thru/or about 60% (W/W) especially preferably. In a sustained release drug, although loadings of a drug change with duration of a kind of drug, a desired medicinal value, and an effect, etc., they are used from about 0.01 about 50% (w/w) to biodegradation nature polymer of a base. Preferably, it is used about 40% (w/w) from about 0.1. It is especially used about 30% (w/w) from about 1 preferably.

[0028]Subsequently, a W/O type emulsified matter manufactured by doing in this way is given to underwater desiccation. This underwater desiccation is performed by removing a solvent in an oil phase, after adding a W/O type emulsified matter into aqueous phase (outer water phase) and making a W/O/W type emulsified matter form. Volume of an outer water phase is generally chosen from about 1 of oil phase volume thru/or about 10,000 times. It is chosen out of about 2 thru/or about 5,000 times still more preferably. It is especially chosen out of about 5 thru/or about 2,000 times preferably. An emulsifier may be added into the above-mentioned outer water phase. As long as this emulsifier can generally form a stable W/O/W type emulsified matter, any may be sufficient as it. Specifically, they are anionic surface-active agents (sodium oleate, sodium stearate, sodium lauryl sulfate, etc.) and a nonionic surfactant (polyoxyethylene sorbitan fatty acid ester), for example. [Tween (Tween)80, Tween (Tween)60, an atlas powder company] Polyoxyethylene-castor-oil derivative [HCO-60, HCO-50, Nikko Chemicals] ****, a polyvinyl pyrrolidone, polyvinyl alcohol, carboxymethyl cellulose, lecithin, gelatin, hyaluronic acid, etc. are mentioned. An emulsifier is polyvinyl alcohol preferably. It may be used combining one kind and some in these emulsifiers. An emulsifier is preferred and polyvinyl alcohol is used. Concentration in the case of use can be suitably chosen from about 0.001 to about 20% (W/W) of range. It is used in about 0.01 to about 10% (W/W) of range still more preferably. It is especially used in about 0.05 to about 5% (W/W) of range preferably. Said osmoregulating chemical may be applied into the above-mentioned outer water phase.

[0029]In a manufacturing method of this invention, when making a W/O/W type

emulsified matter form, it is preferred to adjust viscosity of a W/O type emulsified matter to about 150 cp thru/or about 10,000 cp. . As a method of adjusting viscosity, adjust concentration of biodegradation nature polymer of (1) oil phase, for example. (2). Adjust temperature of (3) W/O type emulsified matter which adjusts a quantitative ratio of aqueous phase and an oil phase. (4) When pouring into an outer water phase (5) W/O type emulsified matter which adjusts temperature of an outer water phase, these methods may be independent, or a method of adjusting temperature of a W/O type emulsified matter with a line heater, an air conditioner, etc., for example may be mentioned, and they may be used, combining. In short in a described method, viscosity of a W/O type emulsified matter in case a W/O type emulsified matter turns into a W/O/W type emulsified matter should just carry out even making it set to about 150 cp thru/or about 10,000 cp. In the above (1), since concentration in a case of adjusting concentration of biodegradation nature polymer of an oil phase changes by kind of biodegradation nature polymer, a kind of organic solvent, etc., it is not determined uniquely, but it is about 10 thru/or about 80% (W/W) preferably. although a quantitative ratio in a case of adjusting a quantitative ratio of aqueous phase and an oil phase is not what is uniquely determined with a kind of drug and quantity, and character of an oil phase in the above (2) -- desirable -- W/O= -- they are about 1% thru/or about 50% (V/V). temperature in a case of adjusting temperature of a W/O type emulsified matter in the above (3) -- about -20 ** thru/or the range of the boiling point of an organic solvent -- desirable -- about 0 ** -- or about 30 ** is about 10 ** thru/or about 20 ** still more preferably. The above (1) and in the case of (2), the stage of adjustment of viscosity of a W/O type emulsified matter can carry out, when manufacturing a W/O type emulsified matter. What is necessary is just to make it bring the same result as the above (3) by adjusting temperature of an outer water phase beforehand in the above (4), when adding a W/O type emulsified matter to an outer water phase. Temperature of an outer water phase does not have about 5 **, does not have preferably about 10 ** of about 30 **, and is about 10 ** thru/or about 20 ** still more preferably about 25 **, for example.

[0030]a method of removing an organic solvent -- the very thing -- it can carry out in accordance with a publicly known method. For example, a method of evaporating an organic solvent, etc. are mentioned, adjusting a degree of vacuum using ordinary pressure or a method of using decompression gradually and evaporating an organic solvent, a rotating evaporator, etc. agitating with a propeller type agitator or a magnetic stirrer.

[0031]Thus, after centrifuging or ****(ing) and isolating preparatively an obtained sustained release drug, for example, a microcapsule, (called a microsphere), A drug of isolation which has adhered on the surface of a microcapsule, a drug maintenance substance, an emulsifier, etc. are repeated several times, and distilled water washes them, and re dispersion is carried out to distilled water etc., and it freeze-dries. A condensation inhibitor may be added in the case of freeze-drying. As this condensation inhibitor, water-soluble polysaccharides, such as mannitol and starch (an example, cornstarch, etc.), mineral, amino acid, protein, etc. are mentioned, for example. It is mannitol preferably [among these]. the mixture ratio (weight ratio) of a microcapsule and a condensation inhibitor -- about 50:1 thru/or about 1:1 -- desirable -- about 20:1 thru/or about 1:1 -- it is about 10:1 thru/or about 5:1 still more preferably. In order to prevent condensation of the particles under washing, a condensation inhibitor may be added to distilled water which is a penetrant remover. As this condensation inhibitor, mineral, such as protein, such as water-soluble polysaccharides, such as mannitol, lactose, grape sugar, and starch (an example, cornstarch, etc.), a glycine, fibrin, and collagen, sodium chloride, and dibasic sodium phosphate, etc. are mentioned, for example. A condensation inhibitor is mannitol preferably.

[0032]After freeze-drying, by request, it may warm under decompression and moisture in a microcapsule and removal of an organic solvent may be performed further. there is

no effect of an excessive amount of initial discharge nature improvements of bioactive peptide at less than glass transition temperature of biodegradation nature polymer which cooking temperature used as a base -- quantity -- if too tepid, danger, such as weld of a microcapsule, modification, disassembly of a physiological active substance, and degradation, will increase. Although cooking temperature cannot generally be said, in consideration of mean particle diameter of the physical properties (an example, a molecular weight, stability, etc.) of biodegradation nature polymer used as a base, bioactive peptide, and a microcapsule, cooking time, a desiccation grade of a microcapsule, a heating method, etc., it can determine suitably. Preferably, it is more than glass transition temperature of biodegradation nature polymer used as a base, and stoving is carried out at temperature of a grade to which each particle of this microcapsule does not adhere mutually. Stoving is more preferably carried out from glass transition temperature of biodegradation nature polymer used as a base in a temperature requirement higher about 30 ** than glass transition temperature. using a differential scanning calorimeter with glass transition temperature in here -- warming -- halfway point glass transition temperature obtained when temperature up is carried out at the speed 10 [per minute] or 20 ** is said.

[0033]Although stoving time also changes with cooking temperature, amounts of microcapsules to process, etc., after temperature of the microcapsule itself generally reaches a predetermined temperature, about 24 thru/or about 120 hours are preferred. Further about 48 thru/or about 120 hours are preferred. Although a heating method in particular is not limited, as long as a microcapsule is a method heated uniformly, what kind of method may be used. As a desirable example of this stoving method, a method of carrying out stoving, for example in a thermostat, a flow tub, the moving bed, or a kiln, a method of carrying out stoving with microwave, etc. are used. In these, a method of carrying out stoving in a thermostat is preferred. As mentioned above, after freeze-drying, by warming a microcapsule under decompression, an organic solvent in a microcapsule is removed efficiently and a microcapsule safe for a living body can be obtained. Thus, organic solvent ullage in an obtained microcapsule is about 100 ppm or less.

[0034]It pharmaceutical-preparation-izes to various dosage forms by using to remain as it is or a microcapsule as a source material, and microcapsules are parenterals (passing membrane agent [uterus / injections to an example, intramuscular, hypodermic, an organ, etc. or an embedding agent, a nasal cavity, the rectum,] etc.), and an oral agent. [Liquids and solutions, such as solid preparations, such as an example, a capsule, granules (an example, hard capsules, an elastic capsule, etc.), and powder medicine, syrups, an emulsion, and suspension] etc. A medicine can be prescribed for the patient as ****. For example, in order to make a microcapsule into injections, a microcapsule -- a dispersing agent (an example, Tween 80, HCO-60, and carboxymethyl cellulose (carboxymethylcellulose sodium is included).) Preservatives, such as sodium alginate (an example, methylparaben, propylparaben, etc.), It is considered as mixture with isotonizing agents (an example, sodium chloride, mannitol, sorbitol, grape sugar, etc.) etc., or it distributes with vegetable oil, such as sesame oil and corn oil, and is considered as sustained-release injections which can actually be used as oily suspension. The particle diameter of a microcapsule should just be a range with which it is satisfied of the degree of dispersion and needle penetration nature, when using it, for example as suspension for injection, for example, the range of about 0.1 to about 500 micrometers is mentioned as mean particle diameter. Preferably, it is the particle diameter of the range of about 1 to about 300 micrometers. It is the mean particle diameter of the range of about 2 to about 200 micrometers still more preferably. When a sustained release drug is a microcapsule, the shape turns into the shape of a ball it was suitable for by needle penetration nature by applying an osmoregulating chemical into an outer water phase as mentioned above. In order to use a microcapsule as sterile preparation, a method of making a manufacture whole process sterile, for example, a method of

sterilizing by a gamma ray, a method of adding an antiseptic, etc. are mentioned, but it is not limited in particular.
[0035]A sustained release drug of this invention can be safely used to mammalians (an example, Homo sapiens, a cow, a pig, a dog, a cat, a mouse, a rat, a rabbit, etc.) by low toxicity. Doses of a sustained release drug are a kind of drug, a content, dosage forms and temporal duration of drug release, and an object illness. [An example, the Alzheimer type dementia, senile dementia, cerebrovascular dementia], etc. Although it changes variously with target animals etc., what is necessary is just an effective dose of a drug. As a dose per time of a drug, when a sustained release drug is one-month pharmaceutical preparation, for example, it can choose out of the range of about 0.01 mg per adult thru/or about 30 mg/kg weight suitably. It can choose out of the range of about 0.05 mg thru/or about 20 mg/kg weight suitably preferably. It can choose out of the range of about 0.05 mg thru/or about 10 mg/kg weight suitably still more preferably. A dose of a sustained release drug per time can be suitably chosen from the range of about 0.1 mg per adult thru/or about 300 mg/kg weight. It can choose out of the range of about 0.5 mg thru/or about 200 mg/kg weight suitably preferably. Frequency of administration can be chosen by 1 time in 1 time and one month, and can choose it in several months suitably at several weeks by a kind of drugs, such as 1 etc. time, a content, dosage forms and temporal duration of drug release, an object illness, a target animal, etc.
[0036]
[Embodiment of the Invention]Although an example, a comparative example, and the example of an experiment are given to below and this invention is explained to it still more concretely, these do not limit this invention. Into following, example, comparative example, and example of experiment % shows weight %, unless it mentions specially.
[Example]
600 mg of acetate of example 1 shrimp RACHIDO was dissolved in 0.6 ml of distilled water. the obtained solution -- a lactic acid-glycolic acid copolymer (it outlines the following PLGA) (the Wako Pure Chem make.) Lot. No.950619, lactic-acid-glycolic-acid composition ratio (mol %): In addition to 80/20 and the solution which dissolved GPC weight-average-molecular-weight:13,000 5.4g in 6 ml of dichloromethane, it mixed for 60 seconds with the small homogenizer (made by KINEMACHIKA), and the W/O emulsified matter was obtained. It pours into 1200 ml of 0 or 1% of 5% mannitol content polyvinyl alcohol (EG-40, product made from Japanese synthetic chemistry) solution beforehand cooled at 16-18 **, after cooling this W/O emulsified matter at 16-18 **, It was considered as the W/O/W type emulsified matter at 9000 rpm using the turbine type homomixer (product made from the formation of a special opportunity). After having agitated the obtained W/O/W type emulsified matter at the room temperature for 3 hours, volatilizing dichloromethane and solidifying a W/O emulsified matter, it centrifuged at 2000 rpm using the centrifuge. Dispersion liquid were further centrifuged for the obtained sediment after re dispersion to distilled water, and washing removal of the releaser thing was carried out. The obtained microcapsule was freeze-dried after re dispersion to a little distilled water, and the microcapsule was obtained as powder. The content of shrimp RACHIDO in a microcapsule was 7.9%. The drug content measured the sample which dissolved a 25-mg microcapsule in 10 ml of acetonitrile 80% by the HPLC method after 5 time dilution.
[0037]The microcapsule was obtained like Example 1 except using example 2PLGA (the Wako Pure Chem make, Lot. No.950923, lactic acid / glycolic-acid composition ratio (mol % ratio): 80/20, GPC weight-average-molecular-weight:12,000). The shrimp RACHIDO content in a microcapsule was 7.9%.
[0038]The microcapsule was obtained like Example 1 except using example 3P LGA (the Wako Pure Chem make, Lot. No.950922, lactic acid / glycolic-acid composition ratio (mol %): 80/20, GPC weight-average-molecular-weight:11,000) (Lot 76). The

shrimp RACHIDO content in a microcapsule was 7.9%.
[0039]400 mg of acetate of example 4 shrimp RACHIDO was dissolved in 0.4 ml of distilled water. The obtained solution is added to the solution which dissolved PLGA(Lot. No.941005 [the Wako Pure Chem make,] lactic-acid [/] glycolic-acid composition ratio (mol %): 85/15, GPC weight-average-molecular-weight:13,000)3.6g in 4 ml of dichloromethane, It mixed for 60 seconds with the small homogenizer (made by KINEMACHIKA), and the W/O emulsified matter was obtained. It pours into 800 ml of 0 or 1% polyvinyl alcohol (EG-40, product made from Japanese synthetic chemistry) solution beforehand cooled at 16-18 **, after cooling the obtained W/O emulsified matter at 16-18 **, It was considered as the W/O/W type emulsified matter at 9000 rpm using the turbine type homomixer (product made from the formation of a special opportunity). Subsequent processes prepared the microcapsule like Example 1. The shrimp RACHIDO content in a microcapsule was 7.6%.
[0040]The microcapsule was obtained like Example 4 using example 5PLGA (the Wako Pure Chem make, Lot. No.K1030, lactic acid / glycolic-acid composition ratio (mol %): 75/25, GPC weight-average-molecular-weight:13,000). The shrimp RACHIDO content in a microcapsule was 7.3%.
[0041]The microcapsule was prepared like Example 4 except using the comparative example PLGA (the Wako Pure Chem make, Lot. No.KCP7784, lactic acid / glycolic-acid composition ratio (mol %): 50/50, GPC weight-average-molecular-weight:13,000). The shrimp RACHIDO content in a microcapsule was 6.9%.
[0042]25 mg of microcapsules obtained in example example 1 of an experiment -- 0.25 ml of carrier fluid (1.25 mg of carboxymethyl cellulose.) It distributed to the distilled water which dissolved 0.5 mg of polysorbate 80, and 12.5 mg of mannitol, and the regions-of-back hypodermic of the 10-week old male SD rat was medicated with 22G hypodermic needle. The microcapsule which slaughters a rat for every fixed time and remains to an administration part is taken out after administration, and, in the bottom, a result is shown for a fixed quantity of shrimp RACHIDO in this taken-out microcapsule in Table 1.
[Table 1]

〔表1〕

時間	エビラチド残存率（%）
1日	94．1
1週	79．2
2週	55．4
3週	34．9
4週	20．0
5週	8．1
6週	5．3

As shown in Table 1, in the microcapsule obtained by this invention manufacturing method, there is almost no initial burst and shrimp RACHIDO is emitted at an almost fixed speed over four weeks.
[0043]The rat was medicated with 25 mg of microcapsules obtained by the example comparative example of comparative experiments like the example of an experiment, the amount of the drug which remains to an administration part was quantified, and the drug release nature from a microcapsule was examined. A result is shown in Table 2.

[Table 2]

〔表2〕

時間	エビラチド残存率（%）
1日	81.1
1週	31.3
2週	2.0
3週	0.0
4週	0.0

As shown in Table 2, when lactic acid / glycolic acid ratio is small, a releasing speed is quick, and as pharmaceutical preparation in which a drug is emitted at a fixed speed in two weeks or one month, it is not suitable.

[0044]

[Effect of the Invention]According to the manufacturing method of this invention, the sustained release drug containing an adrenocorticotrophin derivative or its salt is obtained with easy and good yield. the zero over the long period of time of an adrenocorticotrophin derivative or its salt in the sustained release drug obtained by this manufacturing method -- next discharge is enabled.